Hypoglycaemia following JAK inhibitor treatment in diabetes mellitus patients with rheumatoid arthritis

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Background

Janus kinase (JAK) inhibitors are effective small molecular drugs for rheumatoid arthritis (RA) and other immune mediated inflammatory diseases (IMIDs). JAK inhibitors exert their immunosuppressive effects by suppressing the action of JAK, an intracellular tyrosine. Although infections are the most reported side effects, potential glucose lowering effects in patients with diabetes mellitus (DM) have been described in literature and have also been reported as suspected adverse drug reactions (ADRs) to the National Pharmacovigilance Centre Lareb in the Netherlands (1).

Objective

To assess and describe suspected adverse effects of JAK inhibitors on glucose levels in diabetic patients with rheumatic diseases and other IMIDs, as reported in daily practice.

Method

We describe ADR reports of tofacitinib and baricitinib in the European pharmacovigilance Eudravigilance (EV) database from initiation until 12 January 2021. All ADRs in EV are coded according to the Medical Dictionary for Regulatory Activities (MedDRA). We included all reports indicating hypoglycaemia in patients with reported DM type 1 or 2 or with antidiabetic drugs as concomitant medication. This could include oral antidiabetics as well as insulins.

Results

Table 1. Suspected adverse drug reaction reports indicating hypoglycaemia in diabetic patients using tofacitinib or baricitinib in the Eudravigilance database

	Tofacitinib N (%)	Baricitinib N (%)
Number of reports	15 (100)	17 (100)
Mean age years (range)	65 (56 - 78)	62.2 (48 - 78)
Female gender	13 (87)	13 (76)
Indication for JAK inhibitor		
Rheumatoid arthritis	11 (73)	14 (82)
Unknown	3 (20)	3 (18)
Arthritis	1 (7)	-
Reported adverse drug reaction		
Hypoglycaemia	6 (40)	11 (65)[a]
Decreased blood glucose	9 (60)	6 (35)[a]
Time to onset after start JAK inhibitor[b]		
Within 1 month	6 (40)	3 (18)
2-6 Months	2 (13)	2 (12)
More than 6 months	1 (7)	-
Improvement after action:		
Drug withdrawal	3 (20)[c]	1 (6)[d]
Dose adjustments	-	1 (6)[e]
Other	1 (7)[f]	-

a. In one case of baricitinib, hypoglycaemia as well as decreased blood glucose were reported as adverse drug reactions.
b. Time to onset was unknown in 6 reports of tofacitinib and 12 reports of baricitinib.
c. Tofacitinib withdrawal: 1, sitagliptin withdrawal: 1, tofacitinib and insulin withdrawal: 1.
d. Baricitinib withdrawal
e. Baricitinib; after insulin dose adjustments
f. After tofacitinib withdrawal and insulin dose adjustments

On 12 January 2021 the EV database included 32 ADR reports, concerning 32 diabetic patients, indicating hypoglycaemia associated with the use of JAK inhibitors (15 tofacitinib, 17 baricitinib), out of 32,484 ADR reports in total concerning tofacitinib or baricitinb (Table 1). Most patients (25 patients, 78%) used the JAK inhibitor for rheumatoid arthritis. The suspected ADR with MedDRA Preferred Term 'Hypoglycaemia' was reported for 17 patients and MedDRA Preferred Term 'Decreased blood glucose' was reported for 15 patients. In one case, increased insulin sensitivity was described as suspected ADR of baricitinib. In this case, the insulin dose had to be reduced to prevent hypoglycaemia. Of note, the insulin dose had to be increased after temporary discontinuation of baricitinib and was reduced again after baricitinib was restarted. Additionally, in six cases improvements of glycaemic control were described after discontinuation or dose reduction of the JAK inhibitor or antidiabetic drug. Improvements were also described after unknown action or unchanged treatment with JAK inhibitor in eight cases.

Conclusion

JAK inhibitors may induce hypoglycaemia by increasing insulin sensitivity, and consequently may reduce the need for antidiabetic medication (2-3). Healthcare professionals should be alert for these potential ADRs when starting a JAK inhibitor in patients with DM as comorbidity. More research is needed to support our findings and elucidate the underlying pharmacological mechanisms of this potentially beneficial effect of JAK inhibitors.

References
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